THE IDENTIFICATION OF HIPPOCAMPAL NETWORK FUNCTION

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ABSTRACT

This paper presents an approach to the identification of models characterizing the functional properties of the hippocampal formation. In this approach the network properties are characterized as the composite of input/output functions measured for each subsystem in the network. The characterizing functions are the kernels of a functional power series. The calculation and interpretation of these functions is reviewed, and experimental results are presented. Results of computer simulations are presented based on a parallel computer network consisting of transputers organized according to the architecture of the physiological neuronal network.

INTRODUCTION

We have been investigating an approach to modeling neuronal networks based on a general formulation of the system identification problem, which has the advantage of constructing neuronal network models directly constrained by experimental data. We have been applying this approach to the study of the hippocampal formation (Berger and Sclabassi, 1985; Sclabassi et al, 1988a,b; Berger et al, 1988a,b), a neuronal network which is essential for memory formation. The goal is to develop a fundamental, quantitative, understanding of how learning and memory formation are represented at the network level. The characterizing functions are the kernels of a functional power series expansion. This represents a "black box" approach to system identification (Marmarelis and Marmarelis, 1978) and allows the transformational properties of the network to be studied independently of specific physiological hypotheses.

HIPPOCAMPAL FORMATION

The hippocampal formation consists of the entorhinal, hippocampal and subicular cortices (Berger et al, 1987, 1989). The major projection neurons of these three cortical regions form a serially organized, multisynaptic, closed loop circuit (Figure 1A). Axons of the entorhinal cortex, which form the perforant path, terminate in a laminated fashion on the outer two- thirds of the dendrites of granule cells in the dentate gyrus. Projections from granule cells terminate
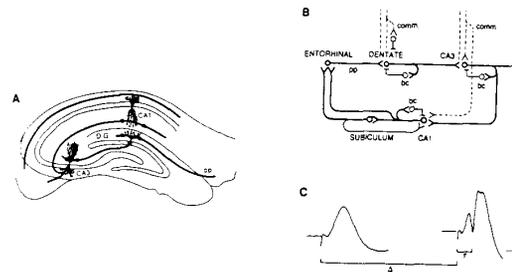

Figure 1: (A) Hippocampal Formation. (B) Schematic Representation. (C) Population Spike as a Function of Δ and τ.

on apical and basal dendrites of pyramidal neurons of the regio inferior (CA3 neurons), which project further to pyramidal neurons of the regio superior (CA1 neurons). The CA1 cell group contacts neurons within the adjacent subicular cortex, and both the regio superior and subiculum send axons to the entorhinal cortex, thus closing a feedback loop to the cells of origin of the perforant path. Numerous short-loop feedback and feedforward circuits are known to exist at each node within this long-loop feedback pathway, forming an inherently complex network structure which may be represented schematically as shown in Figure 1B.

EXPERIMENTAL METHODS

Studies of the $in-vivo$ hippocampus were conducted using male, New Zealand white rabbits. Using halothane anesthesia and standard surgical procedures (Berger et al, 1988a), a bipolar stimulation electrode was positioned in the perforant path and a recording electrode was placed in the cell body layer of the ipsilateral dentate gyrus. Animals were given 1-2 weeks to recover from surgery. Data for all $in-vivo$ experiments described here were collected while animals were unanesthetized, awake, and mildly restrained.

Studies of the $in-vitro$ hippocampal formation were conducted on slices also prepared from male, New Zealand white rabbits. Using appropriate experimental techniques

the hippocampal formation and overlying neocortex were extracted, gently separated, and the hippocampal formation of both hemispheres then blocked under cold oxygenated medium. Slices of tissue 600 μm in thickness were cut containing the dentate gyrus, the CA3 and CA1 regions of the hippocampus, and the intrinsic circuitry that connects these subsystems.

The perforant path of both the *in — vivo* and *in — vitro* preparations was stimulated with the same series of 4064 impulses with inter-impulse intervals drawn from a Poisson distribution having a mean inter-event interval of 500 ms and a range of inter-event intervals of 1-5000 ms. Input/output curves were obtained at the beginning and ending of each experiment to assess stability. Field potentials were amplified and band-pass filtered using low and high frequency limits of 10 Hz to 10 kHz. Amplitudes of the "population spike" components of each field potential were determined by measuring the difference between the peak of the initial positivity and the peak of the subsequent negativity (Figure 1C).

EXPERIMENTAL RESULTS

We assumed that neuroelectric activity observed at the output of the dentate gyrus resulting from perforant path stimulation could be represented in the form of the series expansion:

$$y[x(t)] = \sum_{n=0}^{N} G_n[h_n; x(t)] \qquad (1)$$

where (G_n) is a complete set of mutually-orthogonal functionals (Wiener, 1958), and (h_n) is a set of symmetric kernels which characterize the relationship between the input $x(t)$ and the output $y[x(t)]$. The stimulus function $x(t)$ consisted of electrical impulses characterized as a zero-mean amplitude Poisson process $z(t)$, with a mean rate λ. The kernels (h_n) were obtained using cross-correlation techniques similar to that employed by Lee and Schetzen (1965). The calculations of $h_1(\tau)$, $h_2(\tau, \Delta)$, and $h_3(\tau, \Delta_1, \Delta_2)$ are implemented as averaging procedures (Sclabassi et al, 1988b).

The kernels are interpreted as follows (Figure 2). h_0 is a constant equal to the mean value of the output. The first order kernel (Figure 2A), $h_1(\tau)$, quantifies the average response of the system to the input stimulus, whether or not another stimulus impulse occurs during τ. For a linear system, the first order kernel is the characteristic response function, and all higher order terms are zero. For a nonlinear system, $h_1(\tau)$ is the best linear model; however, it is not the characteristic response of the linear portion of the system, nor is it the response of a nonlinear system to a single impulse, rather it is the "expected" response of the system to the set of impulses conditioned on the time of occurrence of the population spike.

The second order kernel (Figure 2B), $h_2(\tau, \Delta)$, quantifies the deviation in the system's response to a pair of
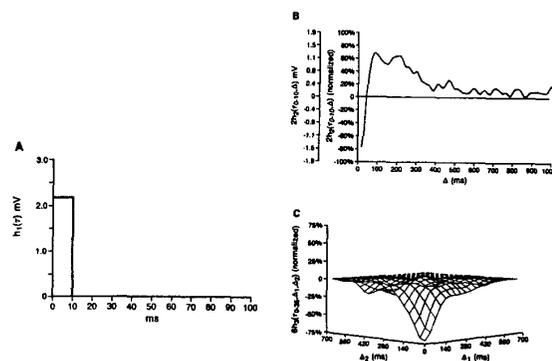

Figure 2: Experimental Kernels

stimulus impulses separated by specified intervals. It is the remainder when the ensemble average over all the impulses is subtracted from the ensemble average over impulses with a specified delay to a preceding impulse (Δ). The result represents nonlinear interactions, i.e., the degree to which the response to the second impulse of a pair is not predicted by superposition. The third order kernel (Figures 2C), $h_3(\tau, \Delta_1, \Delta_2)$ is a quantification of the deviation in the system response to a triplet of impulses separated by specified intervals, and reflects the dependence of system output on different combinations of input intervals, i.e., the degree to which the response to the third impulse of a triplet is not predicted by superposition conditioned on the occurrence of two previous stimuli.

In the *in — vitro* hippocampal slice preparation, second- and third-order nonlinearities are markedly different from the measures obtained in the intact hippocampal formation. A second-order kernel from an *in — vivo* preparation is characterized by almost complete suppression of spike amplitude in response to inter-impulse intervals of 10-20 ms, followed by spike facilitation peaking at about 100 ms and a return toward baseline at 250-350 ms. In contrast, results from slices are characterized by 300-400% facilitation in response to intervals of 10-150 ms. In addition, the *in — vitro* peak decays to baseline 100-200 ms earlier than the *in — vivo* peak.

SIMULATION RESULTS

We have implemented a simulation of the global network properties of the hippocampus using parallel processing technology based on the experimentally derived constraints which the kernels represent (Sclabassi et al, 1989). Convolution integrals utilizing the experimentally determined kernels (through the third order) for each subsystem in the network are represented on the transputers. The network of transputers execute a parallel program which computes a prediction of the input/output behavior from the history of stimuli and the measured kernels using n^{th} order convolutions.

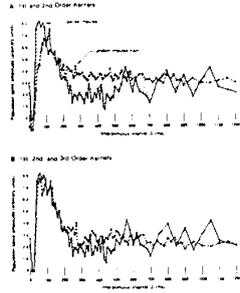A number of detailed simulations have been performed.

Figure 3: Twin-Pulse Simulation Results

In one study, data from the $in-vivo$ intact hippocampal formation was utilized to predict the results of a twin pulse experiment performed on the same animal.

The experimental and simulated results for the twin pulse experiment are summarized in Figure 3, where it can be seen that the predicted data is in excellent agreement with the experimental data for the third order simulation.

DISCUSSION

We have been pursuing an approach to modeling neuronal networks based on identification theory using nonlinear systems analytic procedures. These procedures allow the functional properties of any system of elements to be characterized quantitatively as a set of input/output functions which capture the nonlinear transformations resulting from the interaction among network elements. There are several advantages of utilizing this approach. Functional characteristics of the network that result from interactions among elements are measured directly, so that all mathematical representations of network properties are based on biologically-determined constraints of the system. Input/output data are measured experimentally at the level appropriate to the elemental unit under study and are expressed mathematically in the form of characterizing functions suitable for inclusion in a hierarchical system description. No constraints are placed on the numbers or types of elements that may be contributing to a subsystem output. Network elements are represented explicitly only when their contribution to a subsystem output has been determined through a specific experimental manipulation. Finally, the validity of the model may be verified experimentally. Computer simulations combining the elemental unit models can be used to predict the behavior of any element of the network to a specified input applied at any point in a network.

ACKNOWLEDGEMENTS

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